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PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	30.07.2004
Applicant's or agent's file reference 00850 17719	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/07000	01.07.2003	25.07.2002

Applicant
PHARMACIA ITALIA S.P.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ullrich, J Tel. +49 89 2399-8048

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 00850	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/07000	International filing date *(day/month/year)* 01.07.2003	Priority date *(day/month/year)* 25.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/437		
Applicant PHARMACIA ITALIA S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.01.2004	30.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fazzi, R Telephone No. +49 89 2399-8510

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07000

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-51 as originally filed

Claims, Numbers

1-30 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-12

   because:

   ☒ the said international application, or the said claims Nos. 1-12 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12, 19-30
	No:	Claims	13-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-30
Industrial applicability (IA)	Yes:	Claims	13-30
	No:	Claims	

2. Citations and explanations

   see separate sheet

1) Reference is made to the following documents:

D1: US 2003/073672
D2: WO 02 064574 A
D3: WO 02 12242 A
D4: WO 96 12720 A
D5: KIKUCHI, CHIKA ET AL: 'Tetrahydrothienopyridylbutyltetrahydroben zindoles: new selective ligands of the 5-HT7 receptor' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2002), 12(18), 2549-2552, 16 September 2002, XP002256018
D6: SINGH, P. ET AL: 'Quantitative structure-activity relationship studies on a new class of antihypertensive agents: derivatives of 3-aryl-4,5,6,7-tetrahydro-1H- pyrazolo[4,3-c]pyridine' QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS (1990), 9(1), 29-32, XP001155089
D7: WINTERS, GIORGIO ET AL: 'Synthesis, in vitro [3H]prazosin displacement, and in vivo activity of 3-aryl-4,5,6,7-tetrahydropyrazolo[4,3-c]py ridines, a new class of antihypertensive agents' JOURNAL OF MEDICINAL CHEMISTRY (1985), 28(7), 934-40, XP002256019
D8: RADINOV, R. ET AL: '3-Phenylpyrazolo[4,3-c]pyridine and derivatives: structure determination' JOURNAL OF MOLECULAR STRUCTURE (1987), 158, 99-108, XP009018257
D9: LACKEY K K ET AL: 'The discovery of potent cRaf1 kinase inhibitors' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 3, February 2000 (2000-02), pages 223-226, XP004188821 ISSN: 0960-894X
D10: COHEN P: 'The development and therapeutic potential of protein kinase inhibitors' CURRENT OPINION IN CHEMICAL BIOLOGY, CURRENT BIOLOGY LTD, LONDON, GB, vol. 3, no. 4, August 1999 (1999-08), pages 459-465, XP002216616 ISSN: 1367-5931 cited in the application

1.1) The contents of intermediate documents D1 and D2 will not be taken into consideration in the present PCT phase but could become relevant when entering the European Phase, if the priority of the present application were found invalid.

2) The present application relates to pyrazole-tetrahydro pyridine derivatives active as kinase inhibitors and useful in the treatment of cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

3) Reference to section III

Claims 1-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

4) Novelty (Reference to section V)

D6 discloses substituted 3-aryl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridines (cf. table 1 on page 30), some of which are excluded by the present application by the proviso at the end of claim 13 (cf. claim 13 on page 55, lines 25-28).
However some of the compounds listed in table 1 of D6 fall within the subject-matter of present claim 13 (cf. for instance examples 12-19, 27-28 and 33-36) as said proviso has to be taken into consideration only to exclude compounds possessing hydrogen atoms at all corresponding positions of present R_2 and R_a-R_d substituents.

D7 describes 3-aryl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridines (cf. tables I-III), which overlap with the subject-matter of present claim 13.
In particular, attention is drawn to compounds 12-21 and 27-28 of table I, compounds 40-49 and 55-56 of table II and 61-66 of table III.

Example 4-5 and 9 on page 104 of D8 overlaps as well with the subject-matter of present claim 13.

In view of D6-D8, the subject-matter of claims 13-18 is not new in the sense of Article 33(2) PCT.

5) Inventive step (Reference to section V)

The following observations apply only to those claims, which meet the requirements of Article 33(2) PCT.
The problem to be solved by the present application may be regarded as the provision of further compounds to be used as protein kinase inhibitors (cf. for instance in the treatment of cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders).
D3, which represents the closest state of the art, discloses structurally close compounds, possessing an amino group instead of the current R group.
The skilled person, however, would not have found any incentive from the substitution pattern of D3 in order to arrive at the subject-matter presently claimed.

It is nevertheless to be noticed that **no data** showing that present compounds are actually a solution to the technical problem are given in the application.
Moreover the presence of broad expressions like "optionally substituted" is in contradiction with the basis of qualitative structure-activity-relationships. Taking into account the relevant state of the art and the common knowledge, it appears not to be predictable that all alternatives claimed would achieve the same technical effect.
The Applicant is invited to submit all information available to him to substantiate that all claimed compounds represent an interchangeable solution to the problem underlying this application.

As regards claim 25, the preparation of libraries for the purpose of screening in order to identify chemical entities with desired activities is deemed to fall within the routine work of a person skilled in the art.
Thus the provision of a further library is considered prima facie obvious.
Moreover, in a combinatorial library, most of the compounds do not have the same desired effect because the library is only a tool for identifying those possessing specific properties. Therefore, the technical problem, namely the provision of compounds with a desired activity, is not solved by the library itself, but only by a few members in the library.

However, if the Applicant wishes, the use of a library of claim 25 in order to obtain compounds of formula I could be claimed.

Thus, the subject-matter of claims 1-30 cannot be considered to meet the requirements of Article 33(3) PCT.

6) Industrial applicability (Reference to section V)

For the assessment of the present claims 1-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

7) Further observations

Prodrug: protection cannot be sought for speculative compounds, which have yet to be

prepared and investigated. First of all there is no indication within the application as to what it may be, nor is a prodrug a definable term as regards its structure. The skilled person has no indication as to what falls within this definition, and it should thus be deleted. No analysis of novelty and inventive step has therefore been made for all the compounds which are combinations of "prodrug" and of derivatives of formula 1.